THE SYNTHESIS OF THE INDAZOLE ANALOG OF *DL*-TRYPTOPHAN

BY

RICHARD LESLIE HINMAN

A. B., Columbia College, New York City, 1949

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS
1952

THE SYNTHESIS OF THE INDAZOLE ANALOG OF *DL*-TRYPTOPHAN

BY

RICHARD LESLIE HINMAN

A. B., Columbia College, New York City, 1949

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1952

URBANA, ILLINOIS
1952

ACKNOWLEDGMENT

The author expresses his deep appreciation to Professor Harold R. Snyder for suggesting this problem and for his stimulating advice and cheerful encouragement throughout its execution.

R. UNIV.
BIBLIOTHEEK
LEIDEN

THE SYNTHESIS OF THE INDAZOLE ANALOG OF *DL*-TRYPTOPHAN

Introduction

Prominent among the multitude of organic compounds which have been synthesized and tested for physiological activity are the derivatives of indole. Various analogs of these compounds in which the indole nucleus has been replaced by other cyclic systems have also provoked interest (1). In these investigations indazole, 4,5-benzopyrazole, which has a formal resemblance to indole, has received little attention. The present research was undertaken to re-examine and complete a recently attempted synthesis of *DL* *a*-amino *β*-(3-indazole)-propionic acid, the indazole analog of the important amino acid, *DL*-tryptophan (2).

Since 3-indoleacetic acid and some of its homologs are important in the study of plant growth, it also seemed desirable to synthesize their indazole analogs.

Discussion Of Results

The pivotal intermediate for the synthesis of the indazole analog of tryptophan was the methiodide of 3 dimethylaminomethylindazole. It was prepared *via* the sequence: isatin, 3-indazolecarboxylic acid, N,N-dimethyl-3-indazolecarboxamide, 3-dimethylaminomethylindazole, the desired methiodide. Like the corresponding indole derivative (3), the methiodide smoothly alkylated acetaminomalonic ester, producing ethyl *a* acetamino *a* carbethoxy-*β*-(3 indazole)-propionate. Saponification, decarboxylation, and deacetylation gave *DL*-*a* amino-*β*-(3 indazole)-propionic acid.

In the course of the preparation of N,N-dimethyl-3-indazolecarboxamide, it was found that the isolable intermediate is not 3-indazolecarbonyl chloride, but rather a mixture of two high-melting crystalline compounds. On the basis of combustion analyses, infrared spectra, ebullioscopic measurements of the molecular weight, and other data, it is proposed that one of the products is a cyclic dimer and the other a cyclic trimer, both formed by the self-condensation of 3-indazolecarbonyl chloride. The polymeric compounds react with amines to give the corresponding amides of 3-indazolecarboxylic acid.

An unsuccessful attempt was made to prepare the indazole analog of heteroauxin (3-indoleacetic acid) by way of the reaction of cyanide and the methiodide of 3-dimethylaminomethylindazole.

The alkylation of malonic ester by the methiodide of 3 dimethylaminomethylindazole produced ethyl *a* carbethoxy-β-(3 indazole)-propionate. β-(3-Indazole)-propionic acid was obtained from the acidic hydrolysis of the ester.

γ-(2-Amino 5 bromobenzoyl)-butyric acid is the key intermediate for a proposed synthesis of γ-(3-indazole)-butyric acid. Attempts to prepare the intermediate by the condensation of *p*-bromoacetanilide and glutaric anhydride were unsuccessful.

Several approaches to the synthesis of 3-indazolecarboxaldehyde were investigated. Neither the Stephen reduction of 3-cyanoindazole nor the desulfuration of benzyl 3-indazolethiolcarboxylate gave the desired product. A modification of the Sommelet reaction, carried out with hexamethylene tetramine and the methiodide of 3-dimethylaminomethylindazole, was similarly unsuccessful.

BIBLIOGRAPHY

1. K. Dittmer, Annals New York Acad. Sci., *52*, 1274 (1950).
2. C. B. Thompson, Thesis, Doctor of Philosophy, University of Illinois 1949.
3. H. R. Snyder and C. W. Smith, J. Am. Chem. Soc., *66*, 350 (1944).

VITA

Richard Leslie Hinman was born on March 8, 1927, in Utica, New York. He graduated from Utica Free Academy in 1945 and entered Columbia College in New York City in March of that year. In 1946 he entered the Army of the United States and was assigned to occupation duty in Japan. Upon discharge from the Army in 1947 he re-entered Columbia College and received the degree of Bachelor of Arts in June, 1949. In September, 1949, he entered the Graduate College of the University of Illinois where he held a teaching assistantship in organic chemistry until February, 1951. At that time he was awarded the Visking Corporation Fellowship which he held until June, 1952.